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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/713,373	11/13/2003	Anders Bjorklund	17810-513CON (SCI-13CON)	1621

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EXAMINER	
FALK, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/713,373	BJORKLUND, ANDERS	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) *5-7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/13/03 & 2/27/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The response filed July 26, 2006 has been entered.

Applicant's election without traverse of Group I, Claims 1-4, in the response filed July 26, 2006, is acknowledged. The elected invention is drawn to a method for screening drugs or biological agents.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-7 are pending in the instant application.

Claims 5-7 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention. Election was made **without** traverse in the reply filed on July 26, 2006.

Accordingly, Claims 1-4 are examined herein.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It does not identify the mailing address of each inventor. A mailing address is an address at which an inventor customarily receives his or her mail and may be either a home or business address. The mailing address should include the ZIP Code designation. The mailing address may be provided in an application data sheet or a supplemental oath or declaration. See 37 CFR 1.63(c) and 37 CFR 1.76.
No post office address is provided.

It does not identify the city and either state or foreign country of residence of each inventor. The residence information may be provided on either an application data sheet or supplemental oath or declaration.
The residence is identified as the Wallenberg Neuroscience Center, which does not appear to be an actual residence.

Further, the declaration claims priority to a number of applications for which the conditions for receiving the benefit of priority have not been met. These should be removed from the declaration.

Appropriate correction is required.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

Applicant claims priority to nonprovisional applications 09/339,093, 08/926,313, 09/486,302, and PCT/US98/18597. However, the instant application does not share an inventor in common with any of the aforementioned applications. Anders Bjorklund is the sole inventor named in the instant application and is not a named inventor in any of the aforementioned applications.

Thus, the priority claim does not meet the formal requirements of 35 U.S.C. 120 and priority is not granted. The effective filing date of the instant application is October 20, 1999.

Specification

The disclosure is objected to because it contains an improper priority claim. See above.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 is indefinite in its recitation of "observing changes in size or number of the neurospheres" because there is no step in which neurospheres are formed and further because the term "the neurospheres" lacks antecedent basis. Neurospheres are formed in suspension cultures, but no step

that would lead to the formation of neurospheres is recited. Claim 4 has not been further treated on the merits because no meaningful claim interpretation can be made given the present claim language.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 6,541,255 (Snyder et al., priority to 8/14/1998).

Claim 1 is directed to a method for screening drugs or biological agents which affect proliferation, differentiation or survival of human neural stem cells, comprising: (a) transplanting said human neural stem cells to a first locus of the CNS of a non-human mammal selected from the group consisting of rats and mice; (b) contacting said non-human mammal with at least one drug or biological agent, and (c) determining if said at lease one drug or biological agent has an effect on proliferation, differentiation or survival of said human neural stem cells.

Snyder et al. disclose transplanting human neural stem cells into mice (column 10, lines 43-58) and further determined the results of the transplantation experiments (columns 15-17). Beginning on the day of transplant, cyclosporin was administered daily, thus meeting the limitation of step (b). The reference discloses that the transplanted human neural stem cells differentiated into oligodendrocytes and astrocytes (column 15, lines 49-63) and that the *in vivo* environment induced differentiation into these cell types (column 15, lines 54-63). The transplanted human neural stem cells also differentiated into neurons (column 15, line 64 to column 16, line 34). The reference discloses numerous assays for detecting

differentiation, survival, and proliferation of donor cells (column 10, line 59 to column 12, line 7 and column 17, lines 25-43).

Given that one of skill in the art would have recognized that the survival of transplanted human cells into immunocompetent mice is decreased when immunosuppression is absent, this information serves essentially in the same capacity as a historical control, and therefore the method steps carried out by Snyder et al. results in a determination of the effect of cyclosporin on the survival of human neural stem cells as recited in step (c), which is a positive effect as a result of immunosuppression.

Thus, the claimed method is disclosed in the prior art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,541,255 (**Snyder et al.**, priority to 8/14/1998) and **Kordower et al.** (10/19/1998, In CNS Regeneration: Basic Science and Clinical Advances, (Tuszynski and Kordower, eds.), pp. 159-182, San Diego: Academic Press).

Claim 1 is directed to a method for screening drugs or biological agents which affect proliferation, differentiation or survival of human neural stem cells, comprising: (a) transplanting said human neural stem cells to a first locus of the CNS of a non-human mammal selected from the group consisting of rats and mice; (b) contacting said non-human mammal with at least one drug or biological agent, and (c) determining if said at lease one drug or biological agent has an effect on proliferation, differentiation or survival of said human neural stem cells.

Claim 3 is directed to the method of Claim 1, further comprising the step of inducing differentiation of said human neural stem cells prior to performing step (b).

Snyder et al. disclose transplanting human neural stem cells into mice (column 10, lines 43-58) and further determined the results of the transplantation experiments (columns 15-17). The reference discloses that the transplanted human neural stem cells differentiated into oligodendrocytes and astrocytes (column 15, lines 49-63) and that the *in vivo* environment induced differentiation into these cell types (column 15, lines 54-63). The transplanted human neural stem cells also differentiated into neurons (column 15, line 64 to column 16, line 34). The reference discloses numerous assays for detecting differentiation, survival, and proliferation of donor cells (column 10, line 59 to column 12, line 7 and column 17, lines 25-43).

Kordower et al. (1998) disclose that donor graft survival can be augmented by the concurrent administration of neurotrophic factors into host brain regions receiving the grafts (page 165, paragraph 3). The reference notes that different trophic factors influence specific populations of CNS neurons, and specifically, that epidermal growth factor (EGF) and fibroblast growth factor-2 (FGF-2) promote the growth of neural stem cells in the CNS. The authors emphasize that this fact is of interest with regard to applications in fetal grafting and that supplementing fetal grafts with neurotrophic factors may augment their survival and efficacy (page 165, paragraph 3).

Since one of skill in the art would have been motivated to develop transplantation protocols for therapeutic purposes, the skilled artisan would have been further motivated to identify factors that influence survival, differentiation, and proliferation of human neural stem cells. Snyder et al. already demonstrated that transplantation studies in mice are useful for evaluating the *in vivo* function and capabilities of human neural stem cells and Kordower et al. teaches that the concurrent administration of certain factors may be useful in promoting the survival and function of engrafted cells. Therefore, it would have been obvious to administer such factors, as well as other factors that may adversely affect

engraftment, to evaluate the effect of these factors on the survival, differentiation, and proliferation of human neural stem cells in mice or rats. The skilled artisan would have had a reasonable expectation of success because methods for administering drugs and biological factors to the brains of mice were well developed, as exemplified by the disclosed methods for administering cells to the mouse brain, and because a variety of methods useful for assaying the effect of the factor on the donor cells are clearly disclosed by Snyder et al. As regards the limitations of Claim 3, the step of inducing differentiation prior to performing step (b) is readily obvious because, as Snyder et al. disclose (column 15, lines 54-63), the *in vivo* environment itself induces the differentiation of human neural stem cells into a variety of cell types. Thus, contact with various regions of the brain induces differentiation.

Thus, the claimed methods would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,541,255 (**Snyder et al.**, priority to 8/14/1998), **Kordower et al.** (10/19/1998, In CNS Regeneration: Basic Science and Clinical Advances, (Tuszynski and Kordower, eds.), pp. 159-182, San Diego: Academic Press), and **Ahmed et al.** (1995, J. Neuroscience 15(8): 5765-5778, cited by Applicant on the IDS of 11/13/2003).

Claim 2 is directed to the method of Claim 1, wherein step (c) comprises determining the effects of said biological agent on differentiation of human neural stem cells.

Snyder et al. disclose transplanting human neural stem cells into mice (column 10, lines 43-58) and further determined the results of the transplantation experiments (columns 15-17). The reference discloses that the transplanted human neural stem cells differentiated into oligodendrocytes and astrocytes (column 15, lines 49-63) and that the *in vivo* environment induced differentiation into these cell types (column 15, lines 54-63). The transplanted human neural stem cells also differentiated into neurons (column 15, line 64 to column 16, line 34). The reference discloses numerous assays for detecting

differentiation, survival, and proliferation of donor cells (column 10, line 59 to column 12, line 7 and column 17, lines 25-43).

Kordower et al. (1998) disclose that donor graft survival can be augmented by the concurrent administration of neurotrophic factors into host brain regions receiving the grafts (page 165, paragraph 3). The reference notes that different trophic factors influence specific populations of CNS neurons, and specifically, that epidermal growth factor (EGF) and fibroblast growth factor-2 (FGF-2) promote the growth of neural stem cells in the CNS. The authors emphasize that this fact is of interest with regard to applications in fetal grafting and that supplementing fetal grafts with neurotrophic factors may augment their survival and efficacy (page 165, paragraph 3).

Ahmed et al. (1995) disclose that brain-derived neurotrophic factor (BDNF) enhances the differentiation of CNS stem cells to neuronal cells in the *in vitro* environment.

Since one of skill in the art would have been motivated to develop transplantation protocols for therapeutic purposes, the skilled artisan would have been further motivated to identify factors that influence survival, differentiation, and proliferation of human neural stem cells. Snyder et al. already demonstrated that transplantation studies in mice are useful for evaluating the *in vivo* function and capabilities of human neural stem cells and Kordower et al. teaches that the concurrent administration of certain factors may be useful in promoting the survival and function of engrafted cells. Therefore, it would have been obvious to administer such factors, as well as other factors that may adversely affect engraftment, to evaluate the effect of these factors on the survival, differentiation, and proliferation of human neural stem cells in mice or rats. Since Ahmed et al. disclose that BDNF can be used *in vitro* to stimulate the differentiation of neural stem cells into neurons, one of skill in the art would have been motivated to test the effect of BDNF, as well as other possible differentiation factors, in the context of the *in vivo* environment to determine if it could be used to stimulate differentiation of human neural stem cells to neurons at desired locations in the brain. The skilled artisan would have had a reasonable

expectation of success because methods for administering drugs and biological factors to the brains of mice were well developed, as exemplified by the disclosed methods for administering cells to the mouse brain, and because a variety of methods useful for assaying the effect of the factor on the donor cells are clearly disclosed by Snyder et al.

Thus, the claimed methods would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Claims 1 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Fricker et al.** (7/15/1999, J. Neuroscience 19(14): 5990-6005, cited by Applicant on the IDS of 11/13/03) and **Kordower et al.** (10/19/1998, In CNS Regeneration: Basic Science and Clinical Advances, (Tuszynski and Kordower, eds.), pp. 159-182, San Diego: Academic Press).

Claim 1 is directed to a method for screening drugs or biological agents which affect proliferation, differentiation or survival of human neural stem cells, comprising: (a) transplanting said human neural stem cells to a first locus of the CNS of a non-human mammal selected from the group consisting of rats and mice; (b) contacting said non-human mammal with at least one drug or biological agent, and (c) determining if said at lease one drug or biological agent has an effect on proliferation, differentiation or survival of said human neural stem cells.

Claim 3 is directed to the method of Claim 1, further comprising the step of inducing differentiation of said human neural stem cells prior to performing step (b).

Fricker et al. disclose transplanting human neural stem cells into adult rats and further determined the results of the transplantation experiments. The neural stem cells were obtained from the embryonic human forebrain and expanded in culture in the presence of epidermal growth factor, basic fibroblast growth factor, and leukemia inhibitory factor (abstract). Although the reference refers to the cells as neural progenitor cells, the cells are also known in the art as neural stem cells. The reference discloses

that the transplanted human neural stem cells differentiated into both neuronal and glial phenotypes (abstract). The reference further discloses numerous assays for detecting differentiation, survival, and proliferation of donor cells *in situ* in rat tissue (entire reference).

Kordower et al. (1998) disclose that donor graft survival can be augmented by the concurrent administration of neurotrophic factors into host brain regions receiving the grafts (page 165, paragraph 3). The reference notes that different trophic factors influence specific populations of CNS neurons, and specifically, that epidermal growth factor (EGF) and fibroblast growth factor-2 (FGF-2) promote the growth of neural stem cells in the CNS. The authors emphasize that this fact is of interest with regard to applications in fetal grafting and that supplementing fetal grafts with neurotrophic factors may augment their survival and efficacy (page 165, paragraph 3).

Since one of skill in the art would have been motivated to develop transplantation protocols for therapeutic purposes, the skilled artisan would have been further motivated to identify factors that influence survival, differentiation, and proliferation of human neural stem cells. Fricker et al. already demonstrated that transplantation studies in rats are useful for evaluating the *in vivo* function and capabilities of human neural stem cells and Kordower et al. teaches that the concurrent administration of certain factors may be useful in promoting the survival and function of engrafted cells. Therefore, it would have been obvious to administer such factors, as well as other factors that may *adversely* affect engraftment, to evaluate the effect of these factors on the survival, differentiation, and proliferation of human neural stem cells in mice or rats. The skilled artisan would have had a reasonable expectation of success because methods for administering drugs and biological factors to the brains of mice were well developed, as exemplified by the disclosed methods for administering cells to the rat brain, and because a variety of methods useful for assaying the effect of the factor on the donor cells are clearly disclosed by Fricker et al. throughout the entire reference. As regards the limitations of Claim 3, the step of inducing differentiation prior to performing step (b) is readily obvious because, as Fricker et al. makes abundantly

clear, the *in vivo* environment itself induces the differentiation of human neural stem cells into a variety of cell types. Thus, contact with various regions of the brain induces differentiation.

Thus, the claimed methods would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Fricker et al.** (7/15/1999, J. Neuroscience 19(14): 5990-6005, cited by Applicant on the IDS of 11/13/03), **Kordower et al.** (10/19/1998, In CNS Regeneration: Basic Science and Clinical Advances, (Tuszynski and Kordower, eds.), pp. 159-182, San Diego: Academic Press), and **Ahmed et al.** (1995, J. Neuroscience 15(8): 5765-5778, cited by Applicant on the IDS of 11/13/2003).

Claim 2 is directed to the method of Claim 1, wherein step (c) comprises determining the effects of said biological agent on differentiation of human neural stem cells.

Fricker et al. disclose transplanting human neural stem cells into adult rats and further determined the results of the transplantation experiments. The neural stem cells were obtained from the embryonic human forebrain and expanded in culture in the presence of epidermal growth factor, basic fibroblast growth factor, and leukemia inhibitory factor (abstract). Although the reference refers to the cells as neural progenitor cells, the cells are also known in the art as neural stem cells. The reference discloses that the transplanted human neural stem cells differentiated into both neuronal and glial phenotypes (abstract). The reference further discloses numerous assays for detecting differentiation, survival, and proliferation of donor cells *in situ* in rat tissue (entire reference).

Kordower et al. (1998) disclose that donor graft survival can be augmented by the concurrent administration of neurotrophic factors into host brain regions receiving the grafts (page 165, paragraph 3). The reference notes that different trophic factors influence specific populations of CNS neurons, and specifically, that epidermal growth factor (EGF) and fibroblast growth factor-2 (FGF-2) promote the

growth of neural stem cells in the CNS. The authors emphasize that this fact is of interest with regard to applications in fetal grafting and that supplementing fetal grafts with neurotrophic factors may augment their survival and efficacy (page 165, paragraph 3).

Ahmed et al. (1995) disclose that brain-derived neurotrophic factor (BDNF) enhances the differentiation of CNS stem cells to neuronal cells in the *in vitro* environment.

Since one of skill in the art would have been motivated to develop transplantation protocols for therapeutic purposes, the skilled artisan would have been further motivated to identify factors that influence survival, differentiation, and proliferation of human neural stem cells. Fricker et al. already demonstrated that transplantation studies in rats are useful for evaluating the *in vivo* function and capabilities of human neural stem cells and Kordower et al. teaches that the concurrent administration of certain factors may be useful in promoting the survival and function of engrafted cells. Therefore, it would have been obvious to administer such factors, as well as other factors that may adversely affect engraftment, to evaluate the effect of these factors on the survival, differentiation, and proliferation of human neural stem cells in mice or rats. Since Ahmed et al. disclose that BDNF can be used *in vitro* to stimulate the differentiation of neural stem cells into neurons, one of skill in the art would have been motivated to test the effect of BDNF, as well as other possible differentiation factors, in the context of the *in vivo* environment to determine if it could be used to stimulate differentiation of human neural stem cells to neurons at desired locations in the brain. The skilled artisan would have had a reasonable expectation of success because methods for administering drugs and biological factors to the brains of mice were well developed, as exemplified by the disclosed methods for administering cells to the rat brain, and because a variety of methods useful for assaying the effect of the factor on the donor cells are clearly disclosed by Fricker et al.

Thus, the claimed methods would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

No claims are allowable.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER